Complete Summary

GUIDELINE TITLE

Major depression in adults for mental health care providers.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Major depression in adults for mental health care providers. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Sep. 49 p. [148 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Major depression (single and recurrent major depressive disorders)

This guideline does not pertain to depression within the context of bipolar disorders, adjustment disorders, or medical conditions.

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Psychiatry

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

- To improve the comprehensive evaluation of patients with major depression
- To improve the efficacy of the treatment through diagnosis of depression
- To improve the assessment of treatment and its effectiveness for patients diagnosed with major depression by using a reliable scale at follow-up visit to show symptom reduction (such as the Patient Health Questionnaire [PHQ-9] or Hamilton Depression Scale [HAM-D])
- To improve the adherence and maintenance of appropriate treatments for patients diagnosed with major depression by having follow-up contacts with a health care professional

TARGET POPULATION

Adults greater than 18 years of age with major depressive episodes in an outpatient setting

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Multi-axial assessment, including use of the Global Assessment of Functioning (GAF) scale
2. Assessment of depression using Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision (DSM-IV TR) criteria
3. Assessment of need for hospitalization and suicidal tendencies
4. Chemical abuse/dependency assessment, using the CAGE-AID (AID = Alcohol & Illicit Drugs) screen
5. Evaluation for other mood and anxiety disorders or somatoform disorders

Treatment

1. Patient education
2. Pharmacotherapy
    - Antidepressants
        - Selective serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)

        - Serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine, venlafaxine extended release)
        - Dopamine-norepinephrine reuptake inhibitors (e.g., bupropion, bupropion sustained release)
        - Norepinephrine-serotonin modulator (e.g., mirtazapine)
        - Tricyclic and tetracyclic antidepressants
            - Tertiary amine tricyclics (e.g., amitriptyline, clomipramine, doxepin), imipramine, trimipramine)
            - Secondary amine tricyclics (e.g., desipramine, nortriptyline, protriptyline
            - Tetracyclics (e.g., amoxapine, maprotiline)
        - Serotonin modulators (e.g., nefazodone - black box warning, trazodone - for sleep primarily)
        - Monoamine oxidase inhibitors (MAOIs)
            - Irreversible, nonselective (e.g., phenelzine, tranylcypromine)
            - Reversible MAOI-A (e.g., moclobemide)
        - Selective noradrenaline reuptake inhibitor (e.g., reboxetine)
    - Lithium
    - Antipsychotics
3. Electroconvulsive therapy (ECT)
4. Light therapy
5. Other strategies: augment therapy (including combination of different classes of antidepressants and combination of antidepressants with triiodothyronine, carbamazepine/valproic acid, or risperidone); switch therapy; psychotherapy (specifically, cognitive-behavioral therapy and interpersonal therapy); exercise; herbals; and hospitalization
6. Maintenance therapy and continuing care

MAJOR OUTCOMES CONSIDERED

Diagnosis

Sensitivity and specificity of screening questionnaire

Treatment

- Symptom control
- Relapse (defined as return of symptoms associated with the treated episode)
- Recurrence (defined as the onset of a new episode)
- Functional status (psychological, social, and occupational) and well-being

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline draft, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member medical groups during an eight-week period of "Critical Review".

Each of the Institute's participating medical groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest

modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating medical groups following general implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group: Second Draft

Following the completion of the "Critical Review" period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary, and a written response is prepared to address each of the suggestions received from medical groups. Two members of the Committee on Evidence-Based Medicine carefully review the Critical Review input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of two questions: (1) Have the concerns of the medical groups been adequately addressed? (2) Are the medical groups willing and able to implement the guideline? The committee then either approves the guideline for pilot testing as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Medical groups introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three months. Comments and suggestions are solicited in the same manner as used during the "Critical Review" phase.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Committee on Evidence-Based Medicine reviews the revised guideline and approves it for implementation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

The recommendations are presented in the form of an algorithm with 15 components, accompanied by detailed annotations. The algorithm is provided for Major Depression In Adults For Mental Health Care Providers. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) definitions are provided at the end of the "Major Recommendations" field.

Clinical Highlights

1. A reasonable way to evaluate whether a system is successfully functioning in its diagnosis, treatment plan, and follow-up of major depression is to consider:
    - How well the diagnosis is documented
    - How well the treatment team engages and educates patients/families
    - Does the system document ongoing patient contacts?
    - Does the system measure and document outcomes? (Introduction -see the original guideline document)
2. Presentations for depression include:
    - Multiple somatic complaints, weight gain/loss, mild dementia
    - Multiple (>5/year) medical visits; more than one organ system, with the absence of physical findings
    - Fatigue
    - Work or relationship dysfunction/changes in interpersonal relationships
    - Sleep disturbances

    (Annotation #1)

3. Evaluate depressed patients using all five axes in the Diagnostic and Statistical Manual for Mental Disorders, 4th edition Text Revision (DSM-IV TR) criteria and provide documentation for this evaluation.
    - Axis I: Clinical Disorders, other conditions that may be a focus of clinical attention
    - Axis II: Personality Disorders, borderline intellectual functioning, or mental retardation
    - Axis III: General Medical Conditions
    - Axis IV: Psychosocial and Environmental Problems
    - Axis V: Global Assessment of Functioning

    (Annotation #2)

4. Assess patients who present with safety risks to themselves or others, are unable to care for themselves, or experience psychotic thinking. Those patients should be considered for emergency treatment/hospitalization. (Annotation #5)
5. It is important that treatment involve agreement between the patient and his or her provider involved in managing this condition. Treatment of major depressive episode may involve initiation of pharmacotherapy. Current data does not support the efficacy of one antidepressant or family of antidepressants over another. (Annotation #11)
6. Acute treatment (usually the first 3 months of treatment) refers to treating with antidepressant medication in order to achieve remission of depressive symptoms. Remission is defined as having minimal residual symptoms (Hamilton Depression Scale score less than 7 or Patient Health Questionnaire [PHQ-9] score of 4 or less.) Continuation therapy is the phase where one continues to treat with antidepressants in order to keep the patient free of symptoms for the duration of the current episode. (Annotation #14)
7. If there is less than a 25% reduction in symptoms when evaluated at 4 to 6 weeks, switch to a different medication. If there is a partial response and side effects are not prohibitive, increase the dose. If the patient has not achieved

remission when re-evaluated after an additional 4 to 6 weeks of a treatment regimen, other strategies should be considered. (Annotation #15)

Major Depression In Adults For Mental Health Care Providers Algorithm Annotations

1. Patient Presents with Depressive Symptoms at Mental Health Department

   Clinicians should consider the diagnosis of depression not only when patients present with one of the nine symptoms of a major depressive episode, but also when they present with unexplained somatic symptoms, irritability, anxiety, frequent unnecessary visits to physicians, headaches, and other symptoms.

2. Evaluate Psychiatric Symptoms and Co-Morbidities

   Multiaxial Assessment

   This system involves an assessment on each of five axes. Each axis refers to a different domain of information that may help the clinician assess the patient, plan treatment, and predict outcome.

   Axis I: Clinical disorders, other conditions that may be a focus of clinical attention

   This axis is for listing all diagnoses of mental illness and psychiatric conditions, except for the personality disorders and mental retardation.

   Axis II: Personality disorders, borderline intellectual functioning, or mental retardation

   This axis is for reporting personality disorders, mental retardation developmental learning disorders, and prominent maladaptive personality features and defense mechanisms.

   Axis III: General medical conditions

   If mood disorder is due to a general medical condition, then it is out of the guideline.

   Current general medical conditions which are or may be potentially relevant to the listed Axes I and II disorders are reported in this axis.

   There are no definitive studies which support recommendations for or against routine laboratory or medical screening.

   Axis IV: Psychosocial and environmental problems

Psychosocial and environmental problems which may affect the diagnosis, treatment, and prognosis of Axes I and II are noted here.

When using the "Multiaxial Evaluation Report Form," the clinician should identify the relevant categories of psychosocial and environmental problems and indicate the specific factors involved. If a recording form with a checklist of problem categories is not used, the clinician may simply list the specific problems on Axis IV.

Categories of problems to be considered include:

- Problems with primary support group
- Problems related to the social environment
- Educational problems
- Occupational problems
- Housing problems
- Economic problems
- Problems with access to health care services
- Problems related to interaction with the legal system/crime
- Other psychosocial and environmental problems

Axis V: Global assessment of functioning

Axis V is for reporting the clinician's judgment of the individual's overall level of functioning. This information is useful in rating severity, planning treatment, and measuring its impact, as well as in predicting outcome.

See Appendix A in the original guideline document for the "Global Assessment of Functioning Scale."

Evidence supporting this recommendation is of classes: C, R

3. Does Patient Fit DSM-IV TR Criteria for Major Depressive Episode?

DSM-IV TR criteria for major depressive episode:

A. Five or more of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-congruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3. Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings or restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one); the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

The assessment of major depressive disorders should include the DSM-IV TR numerical rating of the disorder with all 5 digits, thus including a severity rating.

4. Consider Other Mood and Anxiety Somatoform Disorders or Somatoform Disorders

Patients with some depressive disorders who do not meet full DSM-IV TR criteria for major depression often respond positively to antidepressant medication and/or psychotherapy.

Presentations particularly suggestive of an anxiety disorder include:

- Medically unexplained symptoms of autonomic excitation such as:
  - cardiac (chest pain, palpitations, shortness of breath)
  - gastrointestinal (particularly epigastric distress)
  - neurologic (headache, dizziness, paresthesias)
  - panic attacks
- Emergency room visit for medically unexplained somatic symptoms, particularly chest pain

Physical symptoms particularly suggestive of an anxiety disorder include:

- atypical chest pain
- hyperventilation
- irritable bowel syndrome

These depressive syndromes can cause significant impairment, suffering, and disability. Antidepressants should be considered, though the evidence for their efficacy is less well established with these disorders than with major depression. Other depression categories include Dysthymic Disorder and Depressive Disorder NOS (not otherwise specified).

Evidence supporting this recommendation is of classes: A, M

5. Is Patient Unsafe to Self or Others?

Many factors go into the decision to hospitalize a depressed patient. Some of the most salient include:

- Suicidal thoughts and/or plans which make the clinician uncertain of the patient's safety
- Assaultive or homicidal thoughts and/or plans which make the clinician uncertain about the safety of the patient or others
- Inability to care for the self/family
- Psychotic thinking

Assessment of Suicidal Tendencies

There are no good predictors of suicide. History that the clinician should consider includes, but is not limited to:

- Panic attacks and/or severe psychic anxiety
- Depressed mood
- Recent loss by death, divorce, or separation
- Chemical dependency
- Severe hopelessness, or helplessness
- Insomnia
- Severe anhedonia
- Personality disorder and/or physical illness
- Previous history of suicide attempts
- Frequent suicidal ideation
- Concrete suicide plan
- Family history of suicide
- Single status
- Diminished concentration

While it is important to inquire about suicidal tendencies and to account for risk factors, research has shown that all attempts to predict suicidal behavior are somewhat unreliable. Nonetheless, the clinician should routinely address concerns about suicide and document this assessment. The presence of one or more of the factors cited above does not, in and of itself, justify hospitalization or emergency treatment. Clinical judgment as to the likelihood

of imminent harm to the patient or others is the most important consideration.

Evidence supporting this recommendation is of classes: D, R

7. Re-evaluate and Treat for Primary or Secondary Condition

Be aware of comorbidities. Relapse rates may be much higher unless the primary medical illness is simultaneously treated.

Be aware of ongoing mental illness diagnosis or other mental health illnesses and comorbidities.

Some patients presenting with a major depressive episode have a bipolar disorder, for which effective treatment may differ significantly from other depressed patients. When assessing a patient, consider asking about manic or hypomanic episodes.

Has there been a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week?

During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility
6. Increase in goal-directed activity or psychomotor agitation
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences

If these criteria are met, the patient may have a bipolar mood disorder. Treatment for this falls out of the scope of this guideline.

Ask patients with major depression about a history of manic symptoms (abnormally elevated, expansive, or irritable mood). Patients with a history of manic (bipolar) symptoms now presenting with major depression may develop manic symptoms with antidepressant drugs. If other psychiatric problems are present or suspected, involve appropriate professionals. If other psychiatric problems such as psychosis or eating disorders are suspected or present, involve the appropriate professionals.

8. Is Active Chemical Abuse/Dependency Present?

CAGE(AID) Screen (AID = Alcohol & Illicit Drugs)

Have you ever:

C felt you ought to cut down on your drinking or drug use?

A had people annoy you by criticizing your drinking or drug use?

G felt bad or guilty about your drinking or drug use?

E had a drink or used drugs first thing in the morning (eye opener) to steady your nerves or get rid of a hangover or to get the day started?

If substance abuse is present or suspected, consider referral for a chemical dependency assessment.

Evidence supporting this recommendation is of classes: C, R

9. Evaluate and Treat for Chemical Dependency

The medical literature does not support definitive statements about the best way(s) to treat patients who are diagnosed with both major depression and chemical abuse/dependence. The majority of studies reviewed indicate that success in treating dependency on alcohol, cocaine, and other abused substances is more likely if accompanying depression is addressed. Fewer investigators have looked at whether treating chemical dependence is helpful in reducing major depression. There is some evidence that patients with major depression that is secondary to their chemical abuse may have remission of their depressed mood once the chemical dependence is treated. However, it is difficult to separate secondary depression from primary depression that predates or is separate from the chemical use.

Studies to assess the efficacy of concurrent treatment of major depression and substance abuse are limited in number and of variable quality. Although results are not fully consistent, the preponderance of available evidence suggests that pharmacotherapy can be of benefit in treating both chemical abuse and depression in patients who have both disorders. Agents studied include amantadine (a dopamine agonist), desipramine (a tricyclic antidepressant), and fluoxetine (a selective serotonin reuptake inhibitor [SSRI]).

The algorithm reflects the uncertainty in this area. At box #9 it splits into two possible paths. If yes – a depressed patient is felt to be chemically dependent, treatment of the substance abuse should be considered, either before or while treating the depression. However, if no – a depressed patient refuses chemical dependency treatment, or has failed it several times, it is appropriate to focus primarily on the depression. It is reasonable to attempt to treat the depression while continuing to assist the patient to work toward efforts to decrease or eliminate their substance abuse. Continue to ask about addiction issues and to emphasize the need for sobriety. If the patient continues to have depressive symptoms despite antidepressant therapy, this could be pointed out to the patient as one more reason to seek treatment for chemical dependency.

Evaluation and treatment for chemical dependency is beyond the scope of this guideline. A referral may be appropriate.

Evidence supporting this recommendation is of classes: A, C

11. Educate and Engage Patient in Discussion / Treat for Current or Most Recent Episode

Treatment of a major depressive episode may involve the initiation of pharmacotherapy, particularly in the case of moderate and severe episodes. Data do not support the efficacy of one antidepressant or family of antidepressants over another.

For mild to moderate depression, psychotherapy may be elected instead of, or in addition to, pharmacotherapy.

In any case, treatment should involve agreement between the patient and his or her provider (primary care or psychiatry) involved in managing this condition. For recurrent depression, start with the same treatment approach that worked in the previous episode(s) of depression unless prior side effects suggest a different approach.

Evidence supporting this recommendation is of classes: A, M, R

The following subtypes have treatment implications:

Atypical Major Depressive Disorder

Start with an SSRI or a serotonin/norepinephrine reuptake inhibitor (SNRI). Consider using a monoamine oxidase inhibitor (MAOI) as an alterative. Evidence suggests tricyclics are less effective in this subtype.

Evidence supporting this recommendation is of class: A

Major Depressive Disorder with Psychotic Features

Combine a neuroleptic (antipsychotic) with an antidepressant, or use electroconvulsive therapy (ECT).

Evidence supporting this recommendation is of class: R

Seasonal Affective Disorder

Light therapy for seasonal affective disorder is effective, but some issues are unresolved: pathophysiology and usage of medication alone or in conjunction with lights. Responders to light therapy are characterized by hypersomnia, afternoon or evening slump, reverse diurnal variation (evenings worse), and carbohydrate craving.

Evidence supporting this recommendation is of class: R

Melancholic Subtype

Biologic therapy (antidepressants or electroconvulsive therapy) is indicated. Some data suggests that SSRIs are less effective than other antidepressants, but contradictory data exist.

Evidence supporting this recommendation is of classes: C, R

Catatonic Subtype

Hospitalization is appropriate for these patients.

Postpartum Depression

Postpartum blues is a mild and transient episode requiring the passage of time and supportive measures, whereas postpartum depression is potentially severe and prolonged and requires clinical attention. Treatment consists of medication, targeting more frequent obsessional symptoms and supportive therapy. In addition, confusion, disorganization, and psychosis may be present, in which case antipsychotic medicine is indicated.

Evidence supporting this recommendation is of class: R

Additional Treatment Issues:

Antidepressants during pregnancy

Precautions should be taken when treating pregnant patients. No antidepressants administered during pregnancy have been shown to cause birth defects or other complications, yet no studies have proven definitively that antidepressants are safe to administer during pregnancy. The most extensive reviews of outcomes have involved tricyclic antidepressants and fluoxetine; these reviews have not revealed any negative outcomes in the offspring of pregnant mothers taking the medicines.

Evidence supporting this recommendation is of classes: C, M, X

Education About Depression

Patient education is essential for successful treatment of a major depressive episode. Education objectives include:

1. Provide basic information on the causes, diagnosis, treatment, and management of depression.
2. Empower patients to help manage their illness in conjunction with their clinician.
3. Involve the family in educational efforts unless contraindicated.

Selection of an Antidepressant Medication

For antidepressant medications, adherence to a therapeutic dose and meeting clinical goals are more important than the specific drug selected.

SSRI's, venlafaxine, mirtazapine and bupropion

Antidepressant drug selection should be based on:

- the patient's history of response to previous antidepressant medications (if any)
- the patient's comorbid psychiatric or medical conditions
- clinician familiarity with specific antidepressants

The literature clearly supports the effectiveness of tricyclics. Because of associated side effects, they are used less frequently as first-line agents.

Secondary amine tricyclics cause less orthostatic hypotension and sedation than tertiary amine tricyclics.

SSRIs, venlafaxine, mirtazapine and bupropion are frequently chosen as first-line therapy because of simplicity, side effect profiles and community standards.

They generally lack the adverse reactions (anticholinergic, sedative effects) of the tricyclics and cause fewer problems when taken in overdose. However, they may cause headache, nervousness, insomnia, and sexual side effects and may be more expensive as most are not yet available as generics.

The specific side effect profiles and higher costs should be considerations in decisions regarding use of other newer antidepressant medications.

In general, MAOIs should be restricted for patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. Patients suggest MAOIs may be particularly effective. However, in clinical practice, many psychiatrists start with SSRIs in such patients because of the more favorable adverse effect profile.

Medication interactions with antidepressant agents: Many antidepressant agents have clinically significant drug interactions, particularly those agents which undergo cytochrome P450 enzymatic metabolism in the liver. A complete discussion of this topic is beyond the scope of this guideline. Practitioners are advised to consult references such as The Physician's Desk Reference, American Hospital Formulary Service, Epocrates, or Micromedex for more information about drug interactions with specific agents, and to assess the significance of the interaction prior to prescribing antidepressants.

Elderly patients: Because of the potential for decreased renal and hepatic function, concomitant diseases, and medications, the elderly are at higher risk of significant side effects or drug interactions with antidepressant medications. Consider starting at the lowest possible dose and increasing slowly to effective dose or until side effects appear. Tertiary amine tricyclics

should generally be avoided in elderly patients because of the high incidence of orthostatic hypotension, sedation, and cardiac effects with these agents.

Pregnancy: Safety of these agents during pregnancy has not been clearly established. Use only when clearly needed and the potential benefits outweigh the potential hazards to the fetus. US Food and Drug Administration (FDA) Pregnancy Risk Categories: (B): Bupropion, maprotiline. (C): Amitriptyline, amoxapine, citalopram, clomipramine, desipramine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, protriptyline, sertraline, trazodone, trimipramine, venlafaxine. (D): Imipramine, nortriptyline.

Lactation: Antidepressants may appear in breast milk in low concentrations. Because of the long half-life of these drugs and their metabolites, nursing infants may have measurable amounts in their plasma and tissues, such as the brain. This is particularly important during the first few months of life, with immature hepatic and renal function. Because these drugs affect neurotransmitter function in the developing central nervous system, it may not be possible to predict long-term neurodevelopmental effects. Use only when clearly needed and potential benefits outweigh the risks to the nursing infant. (Adapted from American Academy of Pediatrics [AAP] Policy Statement, Transfer of Drugs and Other Chemicals Into Human Milk, Pediatrics 2001;108:776-789).

Commonly Used Antidepressant Medications

For a list of commonly used antidepressant medications, dosing, adverse effects, interactions with other drugs, and precautions, refer to the original guideline document.

For further prescribing information the following drug references may be used:

- The Physicians Desk Reference
- The American Hospital Formulary Service (AHFS)
- Micromedex
- Epocrates

Evidence supporting this recommendation is of class: R

12. Is Patient Responding Adequately? (Evaluate 4-6 Weeks)

The goal is to achieve a significant reduction of symptoms. Assessment includes evaluation of symptoms, work or school attendance and productivity, and quality of interpersonal interactions. There is no professional consensus on what represents an adequate antidepressant trial or patient response. Two of the most common causes of inadequate response are: (1) insufficient dosage; and (2) inadequate duration of treatment.

A patient's response to antidepressant treatment should be evaluated between 4 and 6 weeks. A reasonable criterion for extending the initial treatment is if the patient is experiencing a 25% or grater reduction in

baseline symptom severity. If the medication has been well tolerated, then represcribing and probably raising the dose is recommended. Improvement with psychotherapy is often a bit slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this type of treatment may require 8 to 10 weeks before evaluation.

Evidence supporting this recommendation is of classes: A, M

13. Evaluate Dose, Duration, and Adherence

When patients do not respond to initial antidepressant treatment, clinicians should take the following steps:

1. Re-evaluate the diagnosis
2. Evaluate co-morbid diagnoses

   Substance abuse and personality disorders are often overlooked and confounding. Re-evaluate for the presence of medical conditions.

3. Medication Adherence

   Useful strategies are to review adherence to the medication regimen with the patient and family and check with the pharmacy about frequency of refills.

4. Evaluate dose

   If side effects are tolerable, increase the antidepressant dose. Serum levels of four tricyclic antidepressants are sometimes useful. For nortriptyline, a curvilinear plasma level/therapeutic response relationship exists between 50 and 150 ng/ml. For desipramine, the relationship between serum level and response is linear, with the threshold for therapeutic response being 116 ng/ml (sensitivity 81%, specificity 59%). For imipramine, a linear relationship exists between antidepressant response and serum levels of desipramine plus imipramine of 175 to 350 ng/ml. The data for amitriptyline are weakest and indicate a linear relationship at serum levels of amitriptyline plus nortriptyline of 93 to 140 ng/ml (sensitivity 37%; specificity 80%).

   Other than for the four agents noted above, serum levels are rarely useful for antidepressants, including SSRIs, bupropion, nefazodone, venlafaxine, mirtazapine, and other tricyclics, unless one is checking for compliance.

5. Consider a longer medication trial

   Duration

   Although there is limited scientific data to guide the clinician, an adequate trial of an antidepressant is usually considered to be 4 to 6

weeks. However, duration should not be assessed until the dose is well within the usual therapeutic range. Once that occurs, consider other strategies (see Annotation #14, "Continuation and Maintenance Treatment for 6-12 Months") if there is no response or a minimal response after 4 to 6 weeks.

6. Consider consultation with colleagues

Evidence supporting this recommendation is of classes: A, R

14. Continuation and Maintenance Treatment for 6 to 12 Months

Major depression is now recognized as a recurrent, sometimes chronic, long-term illness. Treatment of major depressive disorder is divided into acute, continuation, and maintenance phases.

Acute treatment, (usually the first 3 months) refers to use of antidepressant medication to strive for remission of major depressive symptoms. Remission is defined as having minimal residual symptoms (Hamilton Depression Scale score less than 7 or PHQ-9 score of 4 or less). Continuation therapy is the phase where one continues to treat with antidepressants in order to keep the patient free of symptoms for the duration of the current episode. By definition, this is considered to be at least 6 months long, but lately more authors are viewing the duration as 6 to 12 months long. Maintenance therapy is designed to prevent recurrence of new or future episodes of depression. Please see Discussion and References #14 in the original guideline document for references to recent evidence-based literature that suggests treating more types of depressed patients with adequate dosages of antidepressants for longer periods is more effective in preventing relapses and reoccurrence. An adequate dose is generally considered to be the same as the dose required in the acute phase of treatment in order to achieve remission.

Recommended guidelines for treatment of depression (treatment duration)

First episode: 6 - 12 months
Second episode: 3 years
Second episode with complicating factors (previous dysthymia): Lifetime
Third episode: Lifetime

Complicating factors are those situations where evidence either shows or suggests higher rates of recurrence after stopping antidepressants and include:

- Pre-existing dysthymia
- Pattern of increasing frequency of episodes
- Inability to achieve remission
- Recurrence of symptoms in response to previously attempted discontinuation

When feasible (e.g., the starting dose is not the same as therapeutic doses), it is recommended that the dose be tapered over a period of weeks to several months when discontinuing an antidepressant.

Psychotherapy

- Outcome studies support the efficacy of several psychotherapeutic approaches (cognitive-behavioral, interpersonal, structured educational group therapy).
- Consider early referral for psychotherapy if psychological and psychosocial issues are prominent and/or patient requests it. Referral for psychotherapy may have maximum benefit as symptom severity diminishes.
- Supportive therapy by the physician in the primary care setting is not the same as a course of psychotherapy with a mental health professional. However, education, support, and reassurance by the physician are critical. Support/reassurance includes asking the patient for his/her ideas regarding the cause of the depression, and about their expectations of recovery. Inform patients with depression that they have a good chance of improving.

Continuation treatment and maintenance treatment should consist of full-dose antidepressant therapy.

Evidence supporting this recommendation is of classes: A, C, D, R, M

For information on exercise and herbals refer to the original guideline document.

Patient Education

1. Successful care of major depression requires active engagement of each patient and their family and ongoing patient education, beginning at the time of diagnosis. It is important for the patient to consider and adopt some self-care responsibilities, which may range from simply demonstrating reliable behavior in taking medications and calling the provider with side effects to agreeing to participate in sessions, journaling, and completing homework, which is necessary for some cognitive behavioral therapies. Written materials are helpful to reinforce information shared during the discussion. Patients who commit to some self-care responsibilities and receive this education compared with those who do not are more likely to continue, rather than prematurely abandon treatment, and are more likely to attain better outcomes. Education topics should include:
    - The cause, symptoms, and natural history of major depression
    - Treatment options (trial and error approach)
    - Information on what to expect during the course of treatment
    - How to monitor symptoms and side effects
    - Follow-up regime (office visits and/or telephone contacts)
    - Early warning signs of relapse or recurrences
    - Length of treatment

2. When antidepressant therapy is prescribed, the following key messages should be highlighted to support medication adherence and completion:
    - Most people need to be on medication at least 6 to 12 months after adequate response to symptoms.
    - It usually takes from 2 to 6 weeks before improvement is seen.
    - Take the medication as prescribed, even after one feels better.
    - Do not stop taking the medication without calling your provider. Side effects can be managed by changes in the dosage or dosage schedule.

Evidence supporting this recommendation is of classes: A, R

Follow-up

Initial Follow-up Contact Intervals (office, phone, other)

If symptoms are severe, weekly contacts are appropriate. Contact should be every 2 to 4 weeks if mild or moderate symptoms are present. This protocol should be in place until remission or best possible response is achieved, then treatment should be spaced out as clinically warranted. Office visits for maintenance medication can occur every 3 to 12 months if everything else is stable.

Referral

Consider involvement of a mental health provider for the following:

- Patient request for psychotherapy
- Presence of severe symptoms and impairment in patient
- Diagnostic question
- Presence of other psychiatric condition (e.g., personality disorder, history of mania)
- Chemical dependency questions
- Clinician discomfort with the case
- Initial treatment does not result in a successful outcome
- Patient's request for more specialized treatment

Evidence supporting this recommendation is of classes: A, M, R

15. Consider Other Strategies

Switch Therapy

If a medication in one family is ineffective, consider changing to a different family of antidepressants. However, failure of a drug in one family does not rule out possible benefit from other drugs in that family. This is particularly true for SSRIs.

- If there is less than a 25% reduction in symptoms when evaluated at 4 to 6 weeks, switch to a different medication. If there is a partial response and side effects are not prohibitive, increase the dose.
- If the patient has not achieved remission when re-evaluated 4 to 6 weeks later, consider:
    - Switching to a different medication, augmentation strategies, adding a new medication
    - Re-evaluating the diagnosis
    - Looking for comorbidities
    - If there are personality disorders present and/or substance abuse, consider referrals. If only on medication, add psychotherapy; if already involved in psychotherapy, change to a different form of therapy.
    - Consider if adequate engagement of patient/family is present and that recommendations are being followed (adherence).
    - Consider obtaining a consultation or referral to other behavioral health specialists.

Evidence supporting this recommendation is of classes: A, D

Augment therapy is used for those situations where patient's depression is either treatment resistant or partially responsive to treatment.

These include:

1. Lithium augmentation with tricyclic antidepressants (TCAs).
2. Lithium augmentation with SSRI (caution - serotonin syndrome).
3. Triiodothyronine (T_3) augmentation of TCA.
4. Stimulant drugs augmentation of TCA/SSRI ("jump-start response").
5. TCA-SSRI combination (caution - elevated TCA level - to be monitored).
6. Bupropion - SSRI combination.
7. Mirtazapine - SSRI combination.
8. Buspirone - SSRI combination.
9. Carbamazepine/valproic acid - TCA combination (caution - may decrease TCA level).
10. Carbamazepine/valproic acid - SSRI combination.
11. Low dose risperidone - SSRI combination.

Evidence supporting this recommendation is of classes: A, C, D, R

Other Biological Therapies

Electroconvulsive treatment is very effective and can sometimes be administered safely in an outpatient setting. Factors to consider for electroconvulsive treatment use in major depression:

1. Agitated depression in elderly patients
2. Antidepressant medications have not been tolerated or pose a significant medical risk.
3. Antidepressant medication trials have not been successful.

4. Electroconvulsive treatment has been successful in previous episodes.
5. Catatonia is present.
6. A rapid response is needed because of severe suicide risk or because the patient's health has been significantly compromised by the depression (i.e., severe cachexia, inability to attend to the activities of everyday living).
7. Psychosis is present despite treatment.

Adjunctive light therapy for patients who present with winter onset depression can also be helpful.

Evidence supporting this recommendation is of classes: A, R

Psychotherapies

Randomized, controlled studies of the efficacy of psychotherapy in the treatment of depression are few. However, comprehensive reviews of these studies support the superiority of time-limited, content and procedure-specific therapies such as cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT). It appears that with mild and moderate levels of major depression, cognitive-behavioral therapy, interpersonal therapy, and antidepressant medications are equally effective. With severe depression, antidepressant medication may be more helpful in the acute phases. Relapse rates are lower with therapy than with medication treatment.

Evidence supporting this recommendation is of classes: A, C, D, M, R,

Hospitalization

Partial or full hospitalization may be indicated in patients who have failed outpatient management.

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study

- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided for Major Depression In Adults For Mental Health Care Providers.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Improved comprehensive evaluation of major depression
- Improved efficacy of the treatment through diagnosis of depression
- Improved targeting of patients for ongoing treatment through Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) severity assessment
- Improved quality of life

- Reduction and remission of symptoms of depression
- Reduction of recurrence of major depression
- Return to previous level of occupational and psychosocial function

POTENTIAL HARMS

- Antidepressant medications pose risk of side effects. These include insomnia, headache, constipation, dry mouth, nausea, sexual dysfunction, dizziness, tremor, orthostatic hypotension, and sedation, among others.
- Lithium augmentation with selective serotonin reuptake inhibitors poses the risk of serotonin syndrome due to elevation of serum levels of the tricyclics.
- Many antidepressant agents have clinically significant drug interactions, particularly those agents which undergo cytochrome P450 enzymatic metabolism in the liver

Subgroups Most Likely to Be Harmed

- Precautions should be taken when treating pregnant patients. No antidepressants administered during pregnancy have been shown to cause birth defects or other complications, yet no studies have proven definitively that antidepressants are safe to administer during pregnancy. The most extensive reviews of outcomes have involved tricyclic antidepressants and fluoxetine; these reviews have not revealed any negative outcomes in the offspring of pregnant mothers taking the medicines.
- Because of the potential for decreased renal and hepatic function, concomitant diseases, and medications, the elderly are at higher risk of significant side effects of drug interactions with antidepressant medications.
- Use tricyclics cautiously in patients with advanced atrioventricular delay.
- Antidepressants may appear in breast milk in low concentrations. Because of the long half-life of these drugs and their metabolites, nursing infants may have measurable amounts in their plasma and tissues, such as the brain. This is particularly important during the first few months of life, with immature hepatic and renal function. Because these drugs affect neurotransmitter function in the developing central nervous system, it may not be possible to predict long-term neurodevelopmental effects.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This clinical guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

RELATED NQMC MEASURES

- Major depression in adults for mental health care providers: percentage of patients with major depression with documentation of multi-axial Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) evaluation.
- Major depression in adults for mental health care providers: percentage of patients with major depression with complete documentation of at least 5 positive Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) symptoms AND at least one of the symptoms is either depressed mood or loss of interest or pleasure.
- Major depression in adults for mental health care providers: percentage of patients with major depressive disorder with documentation of receiving education about major depression.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Major depression in adults for mental health care providers. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Sep. 49 p. [148 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 Feb (revised 2003 Sep)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; e-mail: icsi.info@icsi.org; Web site: www.icsi.org.

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GUIDELINE COMMITTEE

Committee on Evidence-Based Medicine

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Work Group Members: Michael Triangle, MD (Work Group Leader) (HealthPartners/Regions Hospital) (Psychiatry); Craig Anderson, MD (SuperiorHealth Medical Group) (Family Practice); Steve Lucas, MD (HealthPartners Medical Group) (Family Practice); Robert Nesse, MD (Mayo Clinic) (Family Practice); Natalie Retamoza, MD (North Memorial Care System) (Family Practice); Arthur Wineman, MD (HealthPartners Medical Group) (Family Practice); Bruce Hermansen, MD (HealthPartners Medical Group) (Psychiatry); Patricia Evans, PhD (Aspen Medical Group) (Mental Health); Nancy Hammond, PhD (Community-University Health Care Center) (Mental Health); Norman Rasmussen, EdD (Mayo Clinic) (Mental Health); Marjorie Thompson, MA (Community-University Health Care Center) (Mental Health); Kathryn Schultz, PharmD (Allina Medical Clinic) (Pharmacy); Spring Davis, RN (HealthPartners Center for Health Promotion) (Nursing); Lisa Harvey (Park Nicollet Health Services) (Health Education); Nancy Jaeckels (Institute for Clinical Systems Improvement) (Measurement Advisor); Peter Lynch, MPH (Institute for Clinical Systems Improvement) (Evidence Analyst); Barbara Mullikin, MS (Institute for Clinical Systems Improvement) (Facilitator)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, Institute for Clinical Systems Improvement (ICSI) has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform users. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

No work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Major depression in adults for mental health care providers. In: ICSI pocket guidelines. April 2003 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2003 Mar. pp. 250-53.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

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